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Fulbright & Jaworski L.L.P.
Market Square
801 Pennsylvania Avenue, N.W.
Washington, DC 20004-2623

| EXAMINER | |
|---|---|
| RAWLINGS, STEPHEN L | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/670,472 | MA ET AL. | |
| | Examiner | Art Unit | |
| | Stephen L. Rawlings | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,11,27-31,33,45 and 46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-31,33,45 and 46* is/are rejected.

7)☒ Claim(s) *1 and 11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 June 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. The amendment filed April 7, 2008, is acknowledged and has been entered.

2. Claims 1, 11, 27-31, 33, 45, and 46 are pending in the application and are currently under examination.

### *Allowable Subject Matter*

3. The indicated allowability of claims 1, 11, 27-31, and 33 is withdrawn in view of new grounds of objection and/or rejection that follow.

### *Grounds of Objection and Rejection Withdrawn*

4. Unless specifically reiterated below, Applicant's amendment and/or arguments have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed August 10, 2007.

### *Response to Arguments*

5. Applicant's arguments with respect to claim 45 have been considered but are moot in view of the new ground(s) of rejection.

### *New Grounds of Objection*

***Specification***

6. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of such an improperly demarcated trademark appearing in the specification is Taxol™; see, e.g., paragraph [0108] of the published application[1].

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

***Claims***

7. Claims 1 and 11 are objected to because the following informality:

The final parenthesis of the set of parentheses enclosing "SEQ ID NO: 3" in claim 1 was inadvertently deleted by the amendment filed May 9, 2007.

Appropriate correction is required.

8. Claim 31 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 31 is drawn to a composition comprising the tetramer of claim 28, but claim 28 is not drawn to a tetramer.

9. Claim 33 is objected to because the claim recites the term "peptide SEQ ID NO: 3", which presumably is a reference to the earlier recited "peptide that consists of amino acid sequence SEQ ID NO: 3".

It is suggested that this issue be remedied by amending the claim to recite the term "the peptide of SEQ ID NO: 3", as opposed to "peptide SEQ ID NO: 3".

Appropriate correction or rebuttal is required.

[1] U.S. Patent Application Publication No. 2004/0214779-A1.

***New Grounds of Rejection***

***Claim Rejections - 35 USC § 112***

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 27-31 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 27-31 and 33 are vague and indefinite for the following reasons:

(a) Claim 27 is vague and indefinite because the claim recites, "determining a response by said CTL to complexes of [the] HLA-A2 molecule and said peptide wherein a response by said CTL is indicative of its specificity". It is unclear which response by the CTL is necessarily determined in practicing the process that is regarded as the invention by Applicant.

Which response by the CTL is indicative of its specificity for the complex of the HLA-A2 molecule and the peptide? Which responses by the CTL are not so indicative?

In accordance with a recent decision by the Federal Circuit (*Halliburton Energy Services Inc. v. M-I LLC*, 85 USPQ2d 1654, 1658 (Fed. Cir. 2008)):

> 35 U.S.C. § 112, ¶ 2 requires that the specification of a patent "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." Because claims delineate the patentee's right to exclude, the patent statute requires that the scope of the claims be sufficiently definite to inform the public of the bounds of the protected invention, i.e., what subject matter is covered by the exclusive rights of the patent. Otherwise, competitors cannot avoid infringement, defeating the public notice function of patent claims. Athletic Alternatives, Inc. v. Prince Mfg., Inc., 73 F.3d 1573, 1581 (Fed. Cir. 1996) ('[T]he primary purpose of the requirement is 'to guard against unreasonable advantages to the patentee and disadvantages to others arising from uncertainty as to their [respective] rights.'") (quoting Gen. Elec. Co. v. Wabash Appliance Corp., 304 U.S. 364, 369, (1938)). The Supreme Court has stated that "[t]he statutory requirement of particularity and distinctness in claims is met only when [the claims] clearly distinguish what is claimed from what went before in the art and clearly circumscribe what is foreclosed from future enterprise." United Carbon Co. v. Binney & Smith Co., 317 U.S. 228, 236 (1942).

The CTL is capable of a large plurality of measurable responses. Presumably only certain responses by the CTL would provide the practitioner with an indication of the specificity of the CTL for the complex of the HLA-A2 molecule and the peptide; other responses would not.

It is submitted that the claim fails to delineate with the requisite clarity and particularity the steps that must be taken in the practice of the claimed process so as to achieve the claimed objective, namely the identification of a CTL having specificity for the complex of the HLA-A2 molecule and the peptide. As such the claim fails to reasonably apprise the skilled artisan of the metes and bounds of the subject matter that is regarded as the invention so as to permit a determination of infringing subject matter.

(b) Claims 28-31 are indefinite because claim 28 recites, "a plurality of tetramers of an HLA-A2 molecule, a β2 microglobulin molecule, and the peptide of claim 1".

An HLA-A2 molecule, a β2 microglobulin molecule, and the peptide of claim 1 (i.e., three molecules) do not comprise a tetramer, which is necessarily comprised of four components.

Of what other molecule is the tetramer to which the claims are directed composed?

Then, too, a *tetramer* is a term of art, which is used to describe a quarternary complex produced by admixing avidin or streptavidin with biotinylated peptide-MHC molecule complexes at a 4:1 ratio, as first described by Altman et al. (*Science*. 1996 Oct 4; **274**: 94-96). Avidin or streptavidin binds up to four biotin molecules; so when admixed at a 4:1 ratio, four biotinylated peptide-MHC molecule monomers tend to bind to avidin or streptavidin, thus forming the *tetramer*.

Inasmuch as the peptide of claim 1 is not necessarily biotinylated and the first and second binding partners are not necessarily biotin and either avidin or streptavidin, respectively, the complex that is claimed may not be tetrameric; moreover, because the second binding partner, which according to claim 30 is

biotin, is bound to "a plurality of tetramers", it seems that that the claims are not drawn to the *tetramer* described by the prior art. So, if not the tetramer described by the prior art, which is a complex of four biotinylated peptide-MHC molecule monomers bound to avidin or streptavidin, then what is the claimed complex? Again, an HLA-A2 molecule, a β2 microglobulin molecule, and the peptide of claim 1 (i.e., three molecules) do not comprise a tetramer, which is necessarily comprised of four components.

In addition, it is noted that the "first binding partner" to which claim 28 is directed need not be a molecule that is capable of binding four molecules of the "second binding partner"; and it cannot be ascertained how a molecule lacking a plurality of binding sites specifically recognized by a second molecule might bind "a plurality of tetramers of an HLA-A2 molecule, a β2 microglobulin molecule, and the peptide of claim 1".

Accordingly, it is submitted that the claims do not delineate the metes and bounds of the subject matter that is regarded as the invention with the requisite clarity and particularity necessary to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as to permit the skilled artisan to know or determine infringing subject matter.

(c) Claim 33 is indefinite because it cannot be ascertained whether the "tetramers of an HLA-A2 molecule, β2 microglobulin molecule, biotin, and peptide SEQ ID NO: 3" is the *tetramer* described by the prior art or a "tetramer" composed of the four named components.

Again, a *tetramer*, as described by Altman et al. (*supra*), is a quarternary complex produced by admixing avidin or streptavidin with biotinylated peptide-MHC molecule complexes at a 4:1 ratio, such that four biotinylated peptide-MHC molecule monomers bind to the avidin or streptavidin molecule to form the quaternary complex.

Is the claimed "tetramer" the *tetramer* that forms by admixing avidin or streptavidin with biotinylated peptide-MHC molecule complexes at a 4:1 ratio, or is it some other complex, which need not comprise avidin or streptavidin, and

which consists of the four named components (i.e., an HLA-A2 molecule, a β2 microglobulin molecule, biotin, and the peptide)?

Because the claim cannot be unambiguously construed, it is submitted that the claims do not delineate the metes and bounds of the subject matter that is regarded as the invention with the requisite clarity and particularity necessary to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as to permit the skilled artisan to know or determine infringing subject matter.

As an additional matter, claim 33 recites, "determining if a CTL in said CTL-containing sample recognizes said tetramers", but fails to indicate how this determination is necessarily made.

How must the practitioner determine if a CTL in said CTL-containing sample recognizes said tetramers?

If the practitioner cannot ascertain how this determination is made, the practitioner cannot know whether there is any indication that a CTL specific for a complex of the HLA-A2 molecule and the peptide has been detected.

As such, it is submitted that the claim fails to delineate with the requisite clarity and particularity the steps that must be taken in the practice of the claimed process so as to achieve the claimed objective, namely the detection of a CTL specific for a complex of an HLA-A2 molecule and an peptide consisting of the amino acid sequence of SEQ ID NO: 3. As such the claim fails to reasonably apprise the skilled artisan of the metes and bounds of the subject matter that is regarded as the invention so as to permit a determination of infringing subject matter.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 27-31, 33, 45, and 46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making** an

isolated peptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 5, **and for making and using** a tetramer comprised of four biotinylated complexes of a peptide consisting of the amino acid sequence of SEQ ID NO: 3, a β2 microglobulin molecule, and a HLA-A2 molecule, each of which is bound to avidin, **and for using** a method for detecting the presence of a CTL specific for said peptide of SEQ ID NO: 3 in a sample containing CTLs, said method comprising contacting the sample with said tetramer and measuring release of TNF by the CTLs, wherein an increase in the level of TNF by the CTLs, as compared to the level of TNF released by the CTLs in the absence of contact by the tetramer, indicates the sample comprises a CTL specific for said peptide, **does not reasonably provide enablement for using** an isolated peptide consisting of the amino acid sequence of SEQ ID NO: 5, **or for using** a method for determining if a cell presents an HLA-A2 molecule on its surface, said method comprising contacting a sample containing said cell with said peptide and determining binding of the peptide to the cell, wherein binding of the peptide to the cell indicates the cell presents an HLA-A2 molecule on its surface, **or for using** the methods of any of claims 27 and 33, **or for making and using** the products of claims 28-31. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

M.P.E.P. § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is

"undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

(a) With regard to claims 27 and 33, both claims are drawn to processes for determining if a CTL specific for complexes of an HLA-A2 molecule and the peptide of SEQ ID NO: 3 are present in a sample.

In the case of claim 27, the process comprises admixing the sample with an HLA-A2 molecule and the peptide and then determining "a response" by the CTL to complexes of HLA-A2 and the peptide. However, as noted in the above rejection of the claim under 35 U.S.C. § 112, second paragraph, the CTL is capable of a large plurality of measurable responses. Presumably only certain responses by the CTL would provide the practitioner with an indication of the specificity of the CTL for the complex of the HLA-A2 molecule and the peptide; other responses would not.

The specification describes the assessment of the release of TNF by CTL in the presence of a peptide-HLA-A2 complex that is recognized by the T cell receptor of the CTL.

Indeed such an assay is widely described in the prior art for use in determining the presence in a sample of a CTL that is specific to particular complexes of HLA-A2 molecules and peptides; yet other assays, which measure any of the multitude of different "responses" by the CTL specific to the complex

are not so well described, either in this specification or in relevant technical literature of the prior art. Moreover, it does not appear that the specification provides any guidance, direction or exemplification of other assays, apart from the assay that measures the release of TNF by CTL to gauge the presence in a sample of a CTL that is specific to complexes of an HLA-A2 molecule and the peptides described in the application.

For these reasons, as explained in the above rejection of the claim under 35 U.S.C. § 112, second paragraph, it is unclear which responses by the CTL are determined in practicing the process so as to achieve the claimed objective.

Which responses by the CTL are indicative of its specificity for the complex of the HLA-A2 molecule and the peptide? Which responses by the CTL are not so indicative?

As for claim 33, the recites, "determining if a CTL in said CTL-containing sample recognizes said tetramers", but fails to indicate how this determination is necessarily made.

How must the practitioner determine if a CTL in said CTL-containing sample recognizes said tetramers?

Presumably the practitioner must determine if a CTL in the sample recognizes the tetramer by measuring some sort of "response" by the CTL which occurs in the presence of tetramer comprised of a complex of the peptide and HLA-A2 molecule, which is recognized by the T cell receptor presented at the surface of the CTL; but as noted, it appears that the specification merely describes the assessment of the release of TNF by CTL in the presence of a peptide-HLA-A2 complex that is recognized by the T cell receptor of the CTL, as opposed to any other "response" by the CTL.

If the practitioner cannot ascertain how the presence of a CTL, which is specific for the tetramer comprised of the complex of an HLA-A2 molecule and the peptide, is detected, the practitioner could not use the claimed process to achieve the claimed objective without undue and/or unreasonable

experimentation since it would first be necessary to elaborate upon the disclosure to develop a suitable assay for detecting such a CTL in a sample.

Applicant is therefore reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to develop an assay, which measures a "response" by the CTL that is specific for the complex of the HLA-A2 molecule and the peptide and/or tetramers thereof.

Then, with further regard to claim 33, as also noted in the above rejection of the claim under 35 U.S.C. § 112, second paragraph, it cannot be ascertained whether the "tetramers of an HLA-A2 molecule, β2 microglobulin molecule, biotin, and peptide SEQ ID NO: 3" is the *tetramer* described by the prior art or a "tetramer" composed of the four named components.

Again, a *tetramer*, as described by Altman et al. (*supra*), is a quarternary complex produced by admixing avidin or streptavidin with biotinylated peptide-MHC molecule complexes at a 4:1 ratio, such that four biotinylated peptide-MHC molecule monomers bind to the avidin or streptavidin molecule to form the quaternary complex.

Is the claimed "tetramer" is the *tetramer* that forms by admixing avidin or streptavidin with biotinylated peptide-MHC molecule complexes at a 4:1 ratio, or is it some other complex, which need not comprise avidin or streptavidin, and

which consists of the four named components (i.e., an HLA-A2 molecule, a β2 microglobulin molecule, biotin, and the peptide)?

It is imperative that the identity of the claimed tetramer be known, if the process is to be used without undue and/or unreasonable experimentation to achieve the claimed objective, namely the detection of a CTL specific for a complex of an HLA-A2 molecule and the peptide of SEQ ID NO: 3 because according to Altman et al. (supra) if the CTL is present at very low frequency the assay may lack the sensitivity necessary to detect the CTL unless the claimed "tetramer" is the *tetramer* that forms by admixing avidin or streptavidin with biotinylated peptide-MHC molecule complexes at a 4:1 ratio (page 94, column 1). Altman et al. teaches "detection of low-frequency populations of antigen-specific lymphocytes [(e.g., CTLs)] by staining with their cognate antigen has only been demonstrated for B lymphocytes, making use of the high affinity for antigen that many of these cells have" (page 94, column 1). Altman teaches that in general the same approach has failed to detect T cells largely as a consequence of inherently fast dissociation rates of the complexes that form between the T cell receptor and soluble complexes of peptides and MHC molecules, such as HLA-A2 (page 94, paragraph bridging columns 1 and 2). It is for this reason that Altman et al. describes the production of multimeric peptide-MHC molecule complexes (i.e., *tetramers*) that bind to more than one T cell receptor on a specific T cell and thus have correspondingly slower dissociation rates, making the complexes more suitable for use as an immunological stain (page 94, column 3).

Accordingly, if the claimed "tetramer" is not the *tetramer* that forms by admixing avidin or streptavidin with biotinylated peptide-MHC molecule complexes at a 4:1 ratio, but some other complex, which need not comprise avidin or streptavidin, and which consists of the four named components (i.e., an HLA-A2 molecule, a β2 microglobulin molecule, biotin, and the peptide), it is not apparent that such a complex is a suitable immunological stain for detecting

specific T cells since it is expected that the inherently fast dissociation rate will preclude its usefulness.

Notably the specification only describes the use of the *tetramer* that forms by admixing avidin or streptavidin with biotinylated peptide-MHC molecule complexes at a 4:1 ratio, as opposed to any other tetrameric complex consisting of an HLA-A2 molecule, a β2 microglobulin molecule, biotin, and the peptide, in determining the presence of a CTL specific for the complex of the peptide and HLA-A2 molecule.

As such, it is submitted that the specification would not reasonably enable the skilled artisan to practice the claimed invention to achieve the claimed objective without undue and/or unreasonable experimentation.

(b) With regard to claims 28-31, the claims are directed to a complex comprising a "first binding partner" and a "second binding partner", which presumably bind to one another, wherein said second binding partner is bound to "a plurality of tetramers of an HLA-A2 molecule, a β2 microglobulin molecule, and the peptide of claim 1".

However, as explained in the above rejection of the claims under 35 U.S.C. § 112, second paragraph, an HLA-A2 molecule, a β2 microglobulin molecule, and the peptide of claim 1 (i.e., three molecules) do not comprise a tetramer, which is necessarily comprised of four components.

Of what other molecule is the tetramer to which the claims are directed composed?

As the claims do not specify the identity of the fourth component of the claimed tetramer, it cannot be known; and as such, the claimed invention cannot be made and/or used without undue and unreasonable experimentation.

Then, too, as also explained in the preceding paragraphs, a *tetramer* is a term of art, which is used to describe a quarternary complex produced by admixing avidin or streptavidin with biotinylated peptide-MHC molecule complexes at a 4:1 ratio, as first described by Altman et al. (*supra*). Avidin or streptavidin binds up to four biotin molecules; so when admixed at a 4:1 ratio,

four biotinylated peptide-MHC molecule monomers tend to bind to avidin or streptavidin, thus forming the *tetramer*.

According to claim 30 the "first binding partner" is avidin, and the "second binding partner" is biotin.

However, inasmuch as the peptide of claim 1 is not necessarily biotinylated and the first and second binding partners are not necessarily biotin and either avidin or streptavidin, respectively, the complex to which claims 28, 29, and 31 are directed may not be tetrameric.

Moreover, because the second binding partner, which according to claim 30 is biotin, is bound to "a plurality of tetramers", it seems that that the claims are not drawn to the *tetramer* described by the prior art; but if not the *tetramer* described by the prior art, which is a complex of four biotinylated peptide-MHC molecule monomers bound to avidin or streptavidin, of what is the claimed complex comprised, and of what elements is the tetramer to which the claims are directed composed? Again, an HLA-A2 molecule, a β2 microglobulin molecule, and the peptide of claim 1 (i.e., three molecules) do not comprise a tetramer, which is necessarily comprised of four components.

The "first binding partner" to which claim 28 is directed need not be a molecule that is capable of binding four molecules of the "second binding partner"; and for this reason it cannot be determined how the claimed second binding partner might bind "a plurality of tetramers of an HLA-A2 molecule, a β2 microglobulin molecule, and the peptide of claim 1".

Consequently, because the subject matter that is regarded as the invention is not clearly and particularly defined by the claims, it is submitted that the invention could not be made and/or used without undue and/or unreasonable experimentation. What has not been adequately described cannot be made; and what cannot be made cannot be used.

At best, it appears that the specification would provide only a reasonably enabling disclosure for making and using a tetramer comprised of four biotinylated complexes of a peptide consisting of the amino acid sequence of

SEQ ID NO: 3, a β2 microglobulin molecule, and a HLA-A2 molecule, each of which is bound to avidin, which is produced by processes perhaps best described in specification at paragraph [0057] of the published application.

(c) With regard to claims 45 and 46, as discussed in the preceding Office actions the specification fails to show that the peptide of SEQ ID NO: 5, which is a variant of the peptide of SEQ ID NO: 3, binds to HLA-A2.

The peptide of SEQ ID NO: 5 differs from the peptide of SEQ ID NO: 3 by the substitution of the ninth amino acid at the carboxy-terminus of SEQ ID NO: 3 (i.e., valine) by alanine.

As explained in the preceding Office action the prior art teaches the consequence of such variation cannot be predicted; the peptide of SEQ ID NO: 5 may retain the ability of the peptide of SEQ ID NO: 3 to bind to HLA-A2, or it may not.

The specification discloses the peptide of SEQ ID NO: 5 is used in the determination that a cell presents an HLA-A2 molecule on its surface, but such a determination can only be made if the peptide binds to HLA-A2 - if the peptide does not bind to HLA-A2, it cannot be used to determine the presence of an HLA-A2 on the surface of a cell. If the peptide of SEQ ID NO: 5 binds to HLA-A2 but does so very poorly, it is not evident that the peptide can be used to detect the presence of a cell presenting an HLA-A2 molecule on its surface, particularly if the cell presents only one or a few such molecules. Certainly the usefulness of the peptide of SEQ ID NO: 5 hinges upon its affinity for the HLA-A2 molecule.

Ma et al. (*Int. J. Cancer.* 2004; **109**: 698-702) describes a truncated variant of the peptide of SEQ ID NO: 3, which lacks the carboxyl-terminal valine residue of SEQ ID NO: 3; see entire document (e.g., page 701, Figure 5). This truncated peptide apparently has very little ability to stimulate the specific lysis of target cells by CTL, as compared to the peptide of SEQ ID NO: 3 (page 701, Figure 5), which suggests that the carboxyl-terminal valine residue is critical to the ability of the peptide to bind to HLA-A2 molecules presented at the surface of the target cells.

The specification asserts that the peptide of SEQ ID NO: 5, which lacks this critical residue, is capable of binding to HLA-A2, but fails to provide a showing of any factual evidence in support of such an assertion.

The established peptide-class I MHC binding motif for HLA-A2.1 suggests that for optimal binding affinity, a peptide should be 9 or 10 amino acids long and have a small aliphatic residue (preferably L or M) at the second position from the N-terminus (P2) and at the C-terminus (preferably L or V) (P9 or P10)[2].

Again, the peptide of SEQ ID NO: 5 is a variant of the peptide of SEQ ID NO: 3 in which the *preferred* amino acid at position 9 is replaced by an amino acid that is not generally described as a preferred amino acid in terms of the optimal binding of HLA-A2 by a peptide.

This position is supported by Parker et al. (*J. Immunol.* 1992 Dec 1; **149** (11): 3580-3587); see entire document (e.g., page 3581, Table 1). Parker describes a variant of a peptide that binds to HLA-A2 in which the amino at the ninth position (i.e., valine) is replaced by alanine; though the original peptide binds to HLA-A2, the variant did not (page 3581, Table 1).

Thus, the amino acid at 9$^{th}$ position of the nine amino acid peptide (a so-called *anchor* residue) is of prime importance in determining its ability to bind to HLA-A2. The consequence of the substitution of valine by alanine at the ninth position of SEQ ID NO: 3 upon binding to HLA-A2 cannot be predicted, but must be determined empirically.

Accordingly it is submitted that the skilled artisan would not accept the assertion that the peptide of SEQ ID NO: 5 binds to HLA-A2, or that it can be used to determine if a cell present an HLA-A2 on its surface.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enabled the skilled artisan

to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

14. Claims 28-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). Guidelines continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

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[2] See, e.g., Parker et al. (*J. Immunol.* 1992 Dec 1; 149 (11): 3580-3587); entire document (e.g., the abstract).

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

*Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention.*

In this instance, the claims are directed to a complex comprising a "first binding partner" and a "second binding partner", which presumably bind to one another, wherein said second binding partner is bound to "a plurality of tetramers of an HLA-A2 molecule, a β2 microglobulin molecule, and the peptide of claim 1".

However, as explained in the above rejection of the claims under 35 U.S.C. § 112, second paragraph, an HLA-A2 molecule, a β2 microglobulin molecule, and the peptide of claim 1 (i.e., three molecules) do not comprise a tetramer, which is necessarily comprised of four components.

Of what other molecule is the tetramer to which the claims are directed composed?

As the claims do not specify the identity of the fourth component of the claimed tetramer, it cannot be known; and as such, the claimed invention is not adequately described, so as to satisfy the written description requirement,

because skilled artisan could not immediately envision, recognize or distinguish the subject matter that is regarded as the invention.

Then, too, as explained above, a *tetramer* is a term of art, which is used to describe a quarternary complex produced by admixing avidin or streptavidin with biotinylated peptide-MHC molecule complexes at a 4:1 ratio, as first described by Altman et al. (*supra*). Avidin or streptavidin binds up to four biotin molecules; so when admixed at a 4:1 ratio, four biotinylated peptide-MHC molecule monomers tend to bind to avidin or streptavidin, thus forming the *tetramer*.

According to claim 30 the "first binding partner" is avidin, and the "second binding partner" is biotin.

However, inasmuch as the peptide of claim 1 is not necessarily biotinylated and the first and second binding partners are not necessarily biotin and either avidin or streptavidin, respectively, the complex to which claims 28, 29, and 31 are directed may not be tetrameric.

Moreover, because the second binding partner, which according to claim 30 is biotin, is bound to "a plurality of tetramers", it seems that that the claims are not drawn to the *tetramer* described by the prior art; but if not the *tetramer* described by the prior art, which is a complex of four biotinylated peptide-MHC molecule monomers bound to avidin or streptavidin, of what is the claimed complex comprised, and of what elements is the tetramer to which the claims are directed composed? Again, an HLA-A2 molecule, a β2 microglobulin molecule, and the peptide of claim 1 (i.e., three molecules) do not comprise a tetramer, which is necessarily comprised of four components.

Furthermore, neither avidin nor biotin are reasonably deemed representative of the members of the genus of first and second binding partners, which are suitable for use in the production of the claimed complex useful in isolating a CTL.

The "first binding partner" to which claim 28 is directed need not be a molecule that is capable of binding four molecules of the "second binding partner"; and for this reason it is not evident what features characterize the

claimed second binding partner might bind "a plurality of tetramers of an HLA-A2 molecule, a β2 microglobulin molecule, and the peptide of claim 1".

As explained in the above rejection of the claims, it is imperative that the identity of the claimed tetramer be known, if the process is to be used to achieve the claimed objective, namely the detection of a CTL specific for a complex of an HLA-A2 molecule and the peptide of SEQ ID NO: 3 because according to Altman et al. (*supra*) if the CTL is present at very low frequency the assay may lack the sensitivity necessary to detect the CTL unless the claimed "tetramer" is the *tetramer* that forms by admixing avidin or streptavidin with biotinylated peptide-MHC molecule complexes at a 4:1 ratio (page 94, column 1). Altman et al. teaches "detection of low-frequency populations of antigen-specific lymphocytes [(e.g., CTLs)] by staining with their cognate antigen has only been demonstrated for B lymphocytes, making use of the high affinity for antigen that many of these cells have" (page 94, column 1). Altman teaches that in general the same approach has failed to detect T cells largely as a consequence of inherently fast dissociation rates of the complexes that form between the T cell receptor and soluble complexes of peptides and MHC molecules, such as HLA-A2 (page 94, paragraph bridging columns 1 and 2). It is for this reason that Altman et al. describes the production of multimeric peptide-MHC molecule complexes (i.e., *tetramers*) that bind to more than one T cell receptor on a specific T cell and thus have correspondingly slower dissociation rates, making the complexes more suitable for use as an immunological stain (page 94, column 3).

Accordingly, if the claimed "tetramer" is not the *tetramer* that forms by admixing avidin or streptavidin with biotinylated peptide-MHC molecule complexes at a 4:1 ratio, but some other complex, which need not comprise avidin or streptavidin, and which consists of the four named components (i.e., an HLA-A2 molecule, a β2 microglobulin molecule, biotin, and the peptide), it is not apparent that such a complex is a suitable immunological stain for detecting specific T cells since it is expected that the inherently fast dissociation rate will preclude its usefulness.

Notably the specification only describes the use of the *tetramer* that forms by admixing avidin or streptavidin with biotinylated peptide-MHC molecule complexes at a 4:1 ratio, as opposed to any other tetrameric complex consisting of an HLA-A2 molecule, a β2 microglobulin molecule, biotin, and the peptide, in determining the presence of a CTL specific for the complex of the peptide and HLA-A2 molecule.

Thus, at best, it appears that the specification would provide only an an adequate description of a tetramer comprised of four biotinylated complexes of a peptide consisting of the amino acid sequence of SEQ ID NO: 3, a β2 microglobulin molecule, and a HLA-A2 molecule, each of which is bound to avidin, which is produced by processes perhaps best described in specification at paragraph [0057] of the published application.

***Conclusion***

15. No claim is allowed.

16. The art made of record and not relied upon is considered pertinent to Applicant's disclosure. Xu et al. (*J. Immunol. Methods.* 2002; **268**: 21-28) reviews MHC/peptide tetramer-based studies of T cell function. Karanikas et al. (*J. Immunol.* 2003; **171**: 4898-4904) teaches the production of *tetramers*. Dunbar et al. (*Current Biol.* 1998; **8**: 413-416) teaches direct isolation, phenotyping and cloning of low-frequency CTLs from peripheral blood.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephen L. Rawlings/

Stephen L. Rawlings, Ph.D.
Primary Examiner, Art Unit 1643

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